OBSERVATIONS ON ACUTE AND MULTIPLE EXPOSURE TO ANTICHOLINESTERASE AGENTS

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During the past 5 years over 600 cases of exposure to anticholinesterase agents have been studied. These cases have included exposure to various of the insecticides, particularly parathion or TEPP, and also to nerve gas. Because of the large number of exposures and the fact that in some instances as many as 20 or 30 men were brought to the dispensary at one time for treatment, this experience gives some indication of what might be expected if these agents were used in warfare. The purpose of this paper is to present the symptoms, signs and laboratory data to be expected from varying degrees of acute toxicity to these agents; the possible effects of repeated exposures; and the treatment problem presented by a large number of simultaneous exposures.

The chemical formulae of some of these agents are shown in Figure 1. They are all closely related chemically, and are frequently referred to as the organic phosphorous insecticides. Most of those listed are volatile agents and their penetration through the skin is slow, so that the majority of the exposures reported here were of the inhalation type. Some of the new insecticides being developed with an added sulfur radicle such as systox are relatively non-volatile, but are absorbed rapidly from the skin, and their most toxic route of entry is usually through the skin or gastrointestinal tract. While the majority of these insecticides are being used by persons who have had considerable experience with them and are fully aware of their toxicity, such as farmers, greenhouse workers or commercial sprayers, a considerable number have been used by the home gardener or housewife who knows little about them. Approximately 2 years ago when we checked some of the seed stores in the Denver area, we were able

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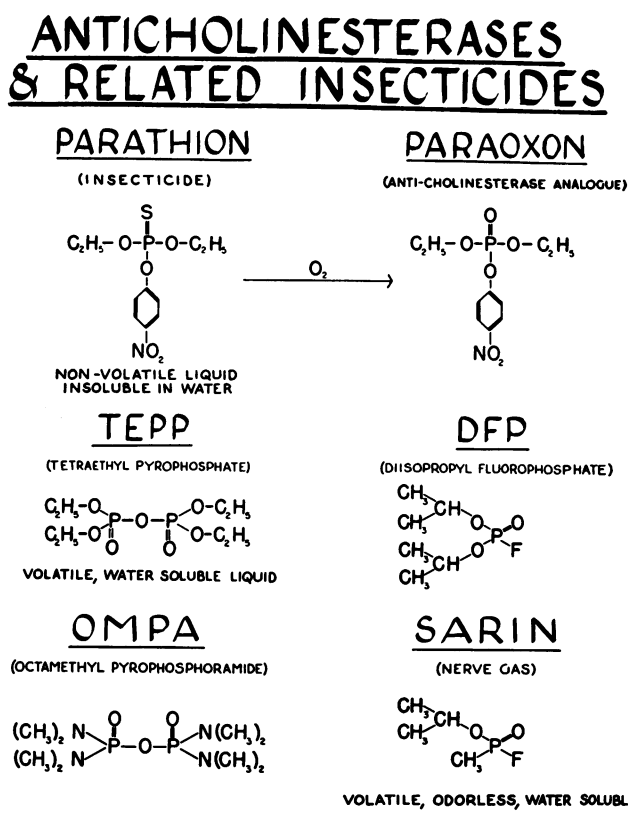

FIG. 1. Shows the chemical formulae for some of the most commonly used anticholinesterase agents. These materials are frequently referred to as the organic phosphorus insecticides.

to pick up at least 2 or 3 insecticides containing these materials at each store.[3] Some of the commercial trade names for parathion include Paraphos, Phenos, Phoskil, Thiophos, Sulphos, E-605, Corothione, Alphamite, Plantthion, Kilphos, Genithion and Paradust. The trade names for TEPP include Fosnex, Plantphos, Vapotone, Tetron, Tetratone, Bladan, Hexamite, Killex and Kilmite.*

These agents combine irreversibly with tissue and blood cholinesterase and inactivate the enzyme. For this reason the symptoms observed are largely referred to the parasympathetic nervous system. Some of these agents also have a "nicotine like" effect which may be responsible for some

* We wish to acknowledge the help of Dr. Donald Spencer of the Federal Wild Life Service in Denver for advice and information regarding toxicity and use of these insecticides in the Colorado area.

of the central nervous system symptoms observed, which are most noticeable in the more severe poisoning. Because of the inhibition of tissue cholinesterase it has been possible to estimate the degree of absorption of these agents by laboratory measurement of the decrease in cholinesterase in the blood. Cholinesterase is found in the plasma as pseudocholinesterase which will hydrolyze not only acetylcholine, but other related compounds, and in the red cell as true cholinesterase which specifically hydrolyzes acetylcholine. The true cholinesterase is the predominant cholinesterase of the central nervous system. A decrease in red cell cholinesterase is considered the best index of significant exposure, and the extent of this decrease tends to correlate closely with the symptoms.

In considering the symptoms and signs observed in these exposures all data has been classified according to the per cent reduction in red cell cholinesterase. This figure is obtained by averaging control measurements made on each individual prior to exposure and then calculating the per cent reduction on the basis of the sample taken immediately after exposure. Cases without good control data were not included in Table I. The symptoms have been subdivided according to the systems affected and then presented as per cent incidence. In the milder cases (less than 25 per cent reduction in cholinesterase) the most common eye signs were miosis and dimness of vision. These occurred in 89.5 per cent and 62 per cent of the cases respectively. Rhinorrhea was observed in 89.5 per cent of cases. Of the respiratory symptoms, the most frequent were cough and constriction of the chest. Salivation was not noted in the Table, but did occur almost as frequently as rhinorrhea. In the milder cases such symptoms as headache, dreams, fatigue, irritability, increased perspiration, dizziness, and muscle twitching occurred infrequently. However, in the more severe cases, the incidence of these symptoms rose very significantly. Anorexia and nausea were noted in 28 per cent of the milder cases and in 62 per cent of the severe cases. Vomiting was a rare symptom in the mild cases, but occurred in 25 per cent of the severe exposures. The incidence of symptoms referable to the chest did not increase significantly with the increasing severity of the exposure. No single symptom occurred in every case except for miosis which was observed in all of the severe exposures. Approximately 150 additional cases have been studied, but were not listed because they had inadequate control cholinesterase determinations.

Sometimes symptom charts do not give as vivid an impression of the exposure as does a brief description in the individual's own words. Interviews with 2 mild exposures and one severe exposure are given below. All interviews were recorded on a tape recorder so they represent the patient's actual words.

TABLE I

Shows the incidence of symptoms in a group of 449 cases of anticholinesterase poisoning. These are grouped according to the per cent reduction in red cell cholinesterase. This serves as an index of the severity of the exposure.

System Involved and Signs or Symptoms	RBC ChE Reduction 0–10%	RBC ChE Reduction 10–25%	RBC ChE Reduction 25–40%	RBC ChE Reduction 40–60%	RBC ChE Reduction over 60%
	% of 169 Cases	% of 153 Cases	% of 78 Cases	% of 33 Cases	% of 16 Cases
Eye					
Miosis	75.2	88.9	92.3	97.0	100
Lacrimation, Pain	29.6	24.2	41.0	48.5	50
Dimness of Vision	44.4	62.0	73.1	69.7	100
Impaired Accommodation	7.1	13.1	10.3	33.3	43.7
Pain on Accommodation	5.9	7.2	11.5	27.3	43.7
Injection Conjunctiva	8.9	13.1	15.4	33.3	62.5
Nose					
Rhinorrhea	84.0	89.5	85.9	93.9	81.3
Respiratory					
Constriction of Chest	81.7	81.7	83.3	75.7	68.7
Cough	66.9	61.4	64.1	69.7	50
Wheezing and Rales	16.0	12.4	16.7	9.1	31.3
Dyspnea	45.0	37.2	35.9	48.5	31.3
C.N.S.					
Headache	43.2	45.7	61.5	75.7	68.7
Dreams, Poor Sleep	33.1	27.4	33.3	54.5	75.0
Fatigability	34.3	31.4	32.0	33.3	31.3
Nervous & Irritable, Mood Changes	23.7	24.2	38.5	39.4	37.5
Increased Perspiration	13.0	17.6	29.5	30.3	62.5
Dizziness	11.2	11.8	15.4	30.3	31.3
Tremor & Twitch, Fasiculation	3.5	3.3	6.4	3.0	25.0
Paresthesia & Cold	5.9	6.5	11.5	21.2	25.0
Gastrointestinal					
Anorexia & Nausea	26.0	28.1	30.8	45.4	62.5
Vomiting	5.3	1.3	2.6	21.2	25.2
Diarrhea	3.5	6.5	6.4	6.0	12.5

Case 24

Mild Exposure—"I noticed I could hardly breathe, seem to me like someone with asthma. We weren't wearing our masks. There was a pain in my chest—hurt when you breathed hard. I had a headache—pain traveled from back to front, over the eye then back of the head."

Case 26

Mild Exposure—"It didn't bother me until we started down here. I got a runny nose, but didn't feel bad. After the antidote I couldn't hold my

eyes steady. In the night, it felt like someone was standing on my chest. I started getting a headache about 8 o'clock last night. This morning, the sun hurt my eyes and increased the headache."

Case 28

Severe Exposure—(The patient came in to the dispensary about 5 minutes after noticing the first symptoms.) "Chest tightened up, coughed, tried taking deep breaths, started coughing bad, got sick to the stomach, nose running, nauseated—vomited a little on the way down here and after I got down here, had a terrific headache. Given a shot of atropine—very nauseated, headache persisted, legs couldn't move good—when laid down seemed to tighten up, when sitting had the same feeling. Given another shot of atropine and homatropine drops in my eyes—still couldn't breathe, headache persisted—given oxygen. Felt better when given oxygen and third shot of atropine. Next morning—sluggish, didn't care about anything. Put me to bed last night—crazy dreams—felt like I was abstracted from myself—would look over at the door and as long as I had my eyes open it was OK, but when I closed my eyes, could see myself standing by the door looking at myself in bed. When closing my eyes, room seemed full of people—when opened no one would be there. Seemed crazy, all mixed up. Also there was something about watches, but I don't remember what it was about. Don't know whether this was when I was asleep, dreaming, or awake. It was all balled up. Aware of this going on, but not all the time—was in a daze—things kind of fuzzy. It was very difficult to understand—was not able to get things through my head as I usually can. When Dr. Gaon told me to come down this morning it took me a little while to realize he was talking to me."

The most severe exposures in our series represent two exposures to parathion. One was a young school teacher working summers for his father on a small truck farm outside Brighton, Colorado.[2] The other was a recent high school graduate working for one of the airplane spraying outfits in Greeley, Colorado.[3] Both of these men had marked respiratory difficulty with significant cyanosis. The first case required suction and oxygen, but no artificial respiration. The second case stopped breathing twice during the first hour after he was brought to the doctor, and required artificial respiration for a significant period of time.

Physical findings exclusive of the miosis and marked secretions were not remarkable. In the mild exposures complaining of chest constriction and cough the examination of the chest was usually negative. With more severe cases, ronchi, wheezing and bubbling rales were heard. Occasionally signs of obstructive breathing were present, and were always associated with cyanosis. Profuse sweating occurred in the more severe exposures.

Hypertension was frequently present, ranging up to 160–170 mms. of mercury systolic pressure.[4, 5] One severe case of parathion poisoning had systolic pressures up to 220 to 240 mm.[3] which persisted through the period of marked respiratory difficulty. In some cases the blood pressure fell especially during the period of marked respiratory difficulty.[2, 6] With increased severity of exposure muscle twitching and fibrillations, coma, convulsions and marked disturbances of the sensorium were observed. The patient lacked orientation as to time, environment and people. Fecal and urinary incontinence occurred occasionally. After the first 24 hours the exposed individual might complain of numbness and muscle pains. Examination revealed hypoesthesia to light touch and pin prick frequently in circumscribed areas, but not confined to definitive nerve distributions. Some patients were unable to remember street and phone numbers, and unable to recognize old friends. They could read accurately, but could not remember what they had read.

In the mild cases the laboratory findings were not remarkable or particularly specific. The most pronounced and specific changes were the plasma and red cell cholinesterase. In the severe parathion exposures cited above, these values dropped to 0. Certainly a decrease below .3Δ pH units seemed to represent a very severe exposure, whereas, a drop to between .3 and .6 indicated moderately severe exposures. In the single acute exposure the severity of symptoms tended to correlate with the extent of the decrease in red cell and plasma cholinesterase values. In the patient exposed to small doses of agent over a several hour period the drop in red cell cholinesterase would be much greater than in the acute exposure and the severity of symptoms less pronounced. However, in individuals who had had some degree of absorption for a period of days prior to the acute onset of symptoms, correlation with the blood cholinesterase was very poor. On many occasions the dispensary staff have attempted to estimate the cholinesterase value from the clinical symptoms and appearance, and now find that they are frequently unable to make a correct evaluation. It has been postulated that especially in cases with slow absorption the blood cholinesterase acts as a buffer combining with the agent and limiting its combination with the cholinesterase of the central nervous system. These agents form an irreversible compound with the cholinesterase and, therefore, the return to normal of these blood values depends on the rate of formation of new serum albumin and red cells.[4, 5] Thus, in a case where the cholinesterase values have dropped to 0, it will take approximately 28 days for the plasma cholinesterase to return to the normal range (.7 to 1.2Δ pH units and 120 days for the red cell value to return to the normal range (.6 to 1.1Δ pH units).[14] This is illustrated by the curve obtained on the first case of parathion poisoning mentioned above (Fig-

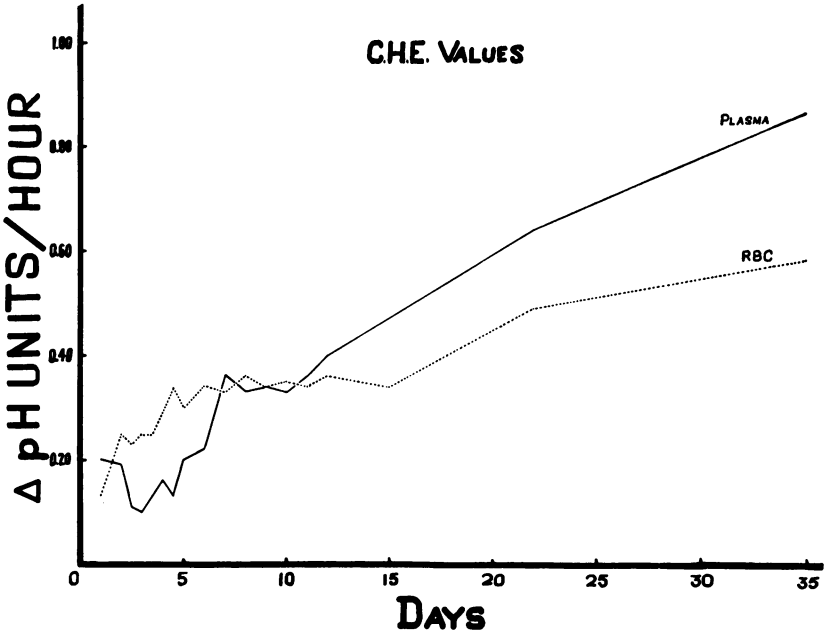

FIG. 2. Shows the rate of recovery of the red cell and plasma cholinesterase values in T.M., a severe case of parathion poisoning.

ure 2). The restoration of red cell and plasma cholinesterase value are seen to be related to the time following exposure.[2]

By correlating the curves for red cell and plasma cholinesterase, one can frequently predict in a person working continuously with these agents the approximate time when he received a significant exposure. Frequently when such a prediction is made, the individual will remember the exact incident which probably accounted for the exposure. For economic reasons, only the red cell cholinesterase is done routinely, but in questionable cases the physician should request both determinations since a high plasma value in the presence of a low red cell value rules out recent exposure. The laboratory determination is based on the change in pH when cells or plasma are incubated with acetylcholine.[7] The cholinesterase activity of the cells or plasma determine the extent of hydrolysis of the acetylcholine and the corresponding pH change of the solution. There are field kits available on the commercial market for determining the cholinesterase activity of blood (these methods employ an indicator rather than a pH meter) which are suitable for differentiation between no change, moderate change and a pronounced decrease. With these kits it takes less than one-half hour to determine the cholinesterase activity and they have proved particularly useful in detecting a severe drop in cholinesterase

activity before symptoms have occurred in field crews of the airplane spraying outfits.

Other laboratory changes produced by exposure to these agents frequently include an elevation of the serum phosphate and blood sugar, a drop in the serum creatinine, and occasionally a significant reduction in the serum potassium.[2, 3] The first case of parathion poisoning mentioned above had a serum potassium of 2.5 mEq/L.[2] The urine on the initial specimen frequently showed a glycosuria and an albuminuria. Subsequent specimens were usually negative. The hematocrit may be elevated, usually 5 per cent, but up to a maximum of 10 per cent. There may be an associated increase in the concentration of serum proteins. A marked hemoglobinuria occurred in one of our cases[2] and a practicing physician in Colorado Springs told us of another case. For this reason a number of red cell fragility tests were done and, while there were some instances of slightly increased fragility, in most cases the test was normal. A significant leukocytosis ranging between 10,000 and 20,000 was a common finding.[3, 4, 5] The urine sometimes contained increased amounts of phosphate and potassium, but this might also be an effect of the atropine used in treatment.[9] The EKG occasionally showed minor variations in T-waves and S-T segments, which became particularly apparent if successive tracings were made over a 2-week period. They appeared to be nonspecific, and probably of no great significance.

Studies of the changes in blood coagulation were made in 21 patients. There was often a prolonged thrombin time, an increased fibrinolytic tendency, a reduced prothrombin activity and a reduced factor V and VII activity. These all returned to normal after varying intervals of time. Such changes would be consistent with slight liver damage. Hypercoagulability was noted in some patients, and perhaps reflected in the beginning or the end of the liver damage phase. Control studies with atropine indicated that this drug did not produce changes of this type.

Atropine blocks effectively many of the "muscarine like" effects of these agents. A great deal of evidence has been presented to show a need for prompt and effective administration of atropine. Apparently these patients tolerate this drug well, and no untoward complications have been observed from large doses. In fact, the literature on parathion poisoning indicates that the highest mortality rate occurred in those cases where atropine therapy was delayed or inadequate.[8] The second case of parathion exposure mentioned above was given in desperation a ½ grain of atropine dissolved in 10 cc. of water.[3] One-tenth of the dose was administered intravenously and the remainder intramuscularly. He improved promptly following its administration. The total dose given over a 24-hour period amounted to 44 mgs. The first case of parathion poisoning

described above received a total of 32 mgs. given over a 24-hour period.[2] Except in the extreme cases our general policy is to administer 2 mgs. stat and repeat every 15 minutes until definite improvement is noted, or full atropine effect obtained.

The other important feature in therapy is the establishment of adequate respiration. This always includes adequate intratracheal suction which is necessary because of the increased bronchial secretions, and may require some form of pressure breathing, such as positive pressure respirator, bellows, mouth to mouth breathing, or manual pressure with an anesthesia machine and bag. The latter methods in addition to their greater availability are cited because the positive pressure required initially may be greater than can be obtained without adjustment from most commercial positive pressure respirators. Insertion of an intratracheal tube or tracheotomy may be necessary in some instances. It is stated that adequate respiration should be established before giving atropine.[15]

One problem on which little data is available in the literature is the possible chronic effect of these agents. Yet according to our own experience this may prove to be of considerable importance as these agents are used more extensively commercially Many individuals who have suffered repeated exposures frequently complain of persistent symptoms. We now have a group of 25 men who have had at least 4 separate and distinct exposures. Some of the symptoms include muscle ache and pain, cramps, numbness, weakness of an arm or leg, etc. Other complaints include increased irritability, marked forgetfulness, confusion in thinking, need for marked concentration in performing tasks such as driving a car, building a radio set, or in taking a correspondence course. Here is a case illustrative of some of the symptoms of which the patients may complain:

Case 9

Severe Exposure—"Get tired—hard to breathe—short of breath, just like I'd run up a hill. This usually happens when I do anything that requires some energy—(fast walking—short runs, etc.). Had a couple of restless nights—nervous. I still get quite nervous—lot more irritable than before. Very absent-minded since last exposure. My mind seems to like to wander—quite marked. I cleaned out garage just after the exposure and now I don't know where I put more than half of the stuff. I distinctly remember trying to store it in places where I could remember, but now I have to go through all the stuff to find it. It was 2 weeks sometimes before I found what I wanted. My thinking seems rather flighty—I've been fairly good in arithmetic, but I can't do it too well in my head now. Can't concentrate on more than one thing at one time. Very frequently hard to understand when someone asks me a question while I'm talking

to some one else. I used to be able to write and be talking to someone at the same time without any trouble, however, now I find it hard to do or can't do it at all—especially just after an exposure. My co-ordination seemed to have been slow. I'd think to do something and it would be quite a while before I'd get it done. Now it's fairly normal. If I anticipate I have to do something I can do it on time. However, when I have to do something unexpectedly I'm very slow at reacting. My arms and legs get much more tired quickly, too."

A group of 37 cases of multiple exposure (3 or more) were reviewed for the signs and symptoms exhibited on their most recent exposure. This group was subdivided according to duration of symptoms. The average incidence of various signs and symptoms is shown in Table II. The duration of symptoms tends to correlate with the degree reduction in red cell cholinesterase. Certain symptoms tend to occur more frequently in the more severe exposures and those with longer duration of symptoms. Many findings not listed in the previous Table were present in this group such as dizziness, fatigability, impaired taste, numbness, irritability and confusion.

In some instances the family or foreman have stated that a man has changed either in his ability to adjust to work or family situations or in his ability to perform jobs around the factory, house, or in recreational activities. We interviewed both the foreman and the 25 men with a history of multiple exposure. Each group listed 6 men with persistent personality or work performance changes, yet only one name was common to both lists.

The general features of the personality change which were most noticeable were forgetfulness and irritability. The symptoms of irritability were described by the subject as being directed toward his children and spouse, rather than toward his foreman and fellow workers. This would go along with the observation of personality problems related to feelings of dependency and inadequacy. The foreman mentioned irritability expressed at work, though the subjects themselves tended to deny such expression of anger and irritability toward their superiors or fellow workers. Forgetfulness generally centered around inability to remember grocery lists with the description that if they wandered through the grocery store and saw the object they were told to bring home, they could then remember perfectly. Other instances were reported of having misplaced their car in a parking lot and then having to walk up and down looking at the rows of automobiles until they recognized their own car. Others described instances of being unable to remember the route to a given destination. For example: one worker had been going to his brother's home every Sunday night for a 10-year period. Two days after an exposure he was

TABLE II

Shows the incidence of symptoms in a group of 37 workers who have suffered 3 or more exposures to these agents. They have been sub-grouped according to duration of symptoms.

Per cent of Patients with Symptom	Duration of Symptoms				
	1 day	3 days	3 to 7 days	7 to 14 days	2 wks. or more
	Four patients	Nine patients	Sixteen patients	Five patients	Three patients
Per cent ChE Reduction	12%	18%	28%	50%	69%
Miosis	25	100	88	100	100
Conjunctivitis	25	33	31	40	66
Eye Ache or Pain	25	77	25	40	33
Dim or Blurred Vision	25	88	69	100	100
Photophobia	25	77	46	60	100
Rhinorrhea	0	88	82	80	66
Chest Constriction	50	88	75	80	66
Cough	0	55	69	80	66
Wheezing	50	11	25	80	33
Anorexia or Nausea	0	55	19	60	66
Vomiting	0	11	6	20	0
Headache	25	66	69	80	66
Disturbed Sleep	0	33	37	60	66
Dreams	0	0	19	40	66
Dizziness	0	33	62	40	66
Fatigability	0	66	62	60	66
Nervous or irritable	0	33	40	60	66
Confused, groggy	0	22	12	20	66
Increased sweating	0	22	37	60	33
Impaired taste or smell	0	22	6	20	66
Pallor	0	22	6	20	33
Sore joints or muscles	0	22	0	20	33
Numbness	0	22	6	20	0

unable to find his brother's house without help. The foremen noticed that when a man was sent to the other end of the building for a specific tool, he would return with the wrong implement. Though sufficient data has not yet been compiled, there are some interesting implications. The occurrence of multiple exposures may be related to basic personality problems and seems to have a component of a repetition compulsion to survive a dangerous situation.

Liver function tests including Van den Bergh, thymol turbidity, plasma cholinesterase, and albumin/globulin ratio were carried out in all cases of multiple exposures. Some patients have been followed every 9 months for a 2-year period. No significant changes have been found in this study up to the present time.

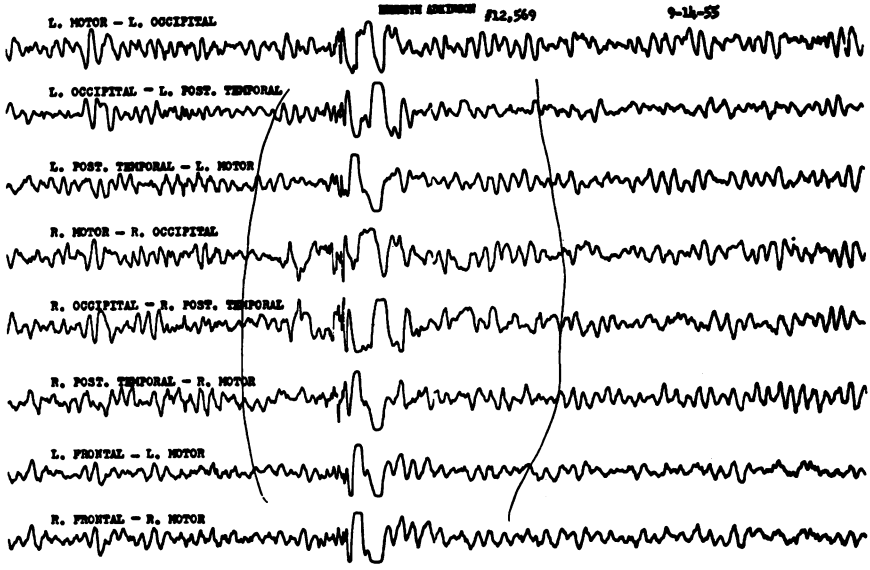

FIG. 3. Shows the EEG changes in a severe case of parathion poisoning. These records were taken in the first month after exposure, but even a year later the above pattern has not changed appreciably. There were no control records on this individual.

Electroencephalograms have been done on a number of these cases, either after severe exposure or after multiple exposures. Focal and paroxysmal changes were observed shortly after exposure which usually disappeared on subsequent records. Grob and Harvey described transient changes in the electroencephalogram with controlled exposure to these agents.[10] In one of our severe cases of parathion poisoning, a rather peculiar type record was obtained initially which has persisted to the present time (a year after the exposure). The record taken one month after exposure is shown in Figure 3. Dr. Harold Locketz commented on the serial records as follows:

"Immediately after the exposure in the first tracing we found paroxysms of high voltage, slow waves (3–6 per second) which occurred both in generalized distribution and in the posterior portions of the brain. In addition, during sleep similar generalized bursts were preceded by asymmetric sharp waves. In subsequent tracings these sharp waves tended to be positive in direction with a comb-like configuration and occurring at a frequency of 14 per second, shifting from side to side. These are the so-called hypothalamic spikes."

While working with these cases it became apparent that some men who had actually had no exposure reported to the dispensary with similar symptoms and complaints. Whenever an accident occurred it was quite

usual to gather in all persons in the vicinity of the accident, and it has even happened that a person working outside the building as the crew came down to the dispensary was brought along. While some of these patients had typical complaints, they showed no physical signs of exposure such as miosis, salivation, rhinorrhea, etc. In most instances their symptoms disappeared within 3 days. The red cell cholinesterase was perfectly normal. However, the red cell cholinesterase may also be normal in cases of true mild respiratory exposure. We have been unable to find any other method for evaluating these cases to rule out definite exposures from those with no possibility of exposure. A similar problem is likely to occur in any mass exposure of civilian populations.

Use of organic phosphorus insecticides in large scale crop spraying operations represents another potential hazard. For the past two summers we have studied members of the ground crew and flying crews of the airplane insecticide spraying companies based in Greeley, Colorado. This group comprised 5 individual companies, each employing from 10 to 30 men. During the spraying season they would start crop spraying at dawn, take a brief rest period at high noon if wind conditions were not favorable, and then continue until dusk. Concentrated parathion 25 per cent, sometimes 40 per cent, and occasionally 80 per cent was diluted to a 2 per cent spraying solution. A 2 per cent dusting mixture of parathion was also used. This was loaded on the planes by the ground crew and the pilot then took off and required approximately 20 minutes to spray this load on the field. As soon as he returned the plane was again loaded and the whole operation repeated. One other member of the group, namely, the man who marks out the lanes in the spraying area would also come in contact with the parathion. Use of parathion which is particularly effective against the beet and bean beetles was usually confined to a period from late June to mid-August. In 1955 there was one extreme exposure among this group and several mild exposures. In summer of 1956 there were 5 moderately severe exposures. Following the first significant exposure each summer, requests were made that we measure the blood cholinesterase of other crew members. The results are shown in Table III listing the number falling in each category. The normal values for red cell cholinesterase are .6 to 1.1Δ pH units.[14] Thirty of the 44 men or 68 per cent had values below normal which was suggestive of some degree of exposure to parathion. Two men had extremely low values, one of these was admitted to the hospital that evening and the other the next day. The other 4 men had sufficient reduction in cholinesterase to be classified in the severe exposure category. All denied any symptoms at the time blood samples were taken.

The normal range for plasma cholinesterase is .7 to 1.2 ΔpH units.[14]

TABLE III

Shows range of red cell and plasma cholinesterase values obtained in men working with parathion in airplane spraying outfits during the summers of 1955 and 1956.

ChE Value, Delta pH units	Red Cell ChE, No. Patients	Plasma ChE, No. patients
.0 - .20	2	1
.20- .40	4	4
.40- .60	24	9
.60- .80	13	15
.80-1.20	1	15

Fourteen had values below .6 and an additional 7, or a total of 21 had values below the normal range (.7 ΔpH units). Thus 9 men had reduced red cell cholinesterase but normal plasma values. These men had probably suffered a definitive exposure at an earlier date, and sufficient time had elapsed for restoration of the plasma cholinesterase (approximately 1 month) but not for restoration of the red cell cholinesterase.

The finding of a low red cell cholinesterase on routine blood examinations presents a serious problem to the physician. Should these men be removed from work, watched carefully, or sent to the hospital? In the case of the 2 men with the lowest values serious symptoms appeared within 48 hours. The other men were watched carefully, but never developed signs of acute toxicity. However, if repeat examinations in one week had shown a further drop in the red cell cholinesterase, then certainly the men should have been removed from any possibility of further exposure. There is little concrete evidence to indicate that men with low blood cholinesterase values are more susceptible to acute exposure but certainly loss of buffering action of the blood might permit more widespread entrance of the agent into the tissues.

This data also emphasizes the value of the cholinesterase measurement in demonstrating whether an individual working with these agents is suffering appreciable absorption. Certainly a low cholinesterase value warrants a distinct revision of work technique even if it does not mean removing the man from work. Furthermore, this man should be checked periodically as long as he continues to work with these agents because if the red cell cholinesterase continues to drop, then certainly removal from any further contact with the insecticide is indicated. Exposure, without symptoms sufficient to require medical attention, may still impair work efficiency especially in critical jobs such as those of a pilot. Last summer a pilot for one of the spraying outfits had a crack-up and the question arose as to whether his judgment had been impaired by undetected exposure. Blood cholinesterase values were consistent with such a hypothesis. Similar experiences and problems have been reported by other investigators.[11, 12, 13]

SUMMARY

The symptoms and physical findings observed in over 600 cases of exposure to anticholinesterase agents have been presented. The cases were divided according to severity of exposure as indicated by the per cent reduction in red cell cholinesterase. No deaths occurred in this group. The laboratory findings included a reduction in red cell and plasma cholinesterase, a leukocytosis and in more severe cases an elevation in the hematocrit and in the serum phosphate and glucose and occasionally a hypopotassemia. The urine showed glycosuria, albuminuria and increased excretion of potassium and phosphate. In some cases changes in blood coagulation were observed and measurements of the definitive factors involved were presented. Persistent symptoms occurred in the more severe exposures and in those with multiple exposures, and included forgetfulness, irritability and confused thinking. Adequate therapy includes maintenance of adequate respiration and large doses of atropine. The use of the red cell and plasma cholinesterase determination to evaluate subclinical exposure in men working with these agents was discussed. Changes in the electroencephalogram were observed but were usually non-specific. The problem of what might be expected during mass exposure to these agents was emphasized.

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DISCUSSION

Dr. Harvey (Baltimore): During the past ten years, as Dr. Holmes indicated, we have been utilizing the very highly specific activity of these compounds on cholinesterase to study the normal functions of these enzymes. During that period, we have had the opportunity to observe a number of practical problems involved in relation to exposure to these compounds.

I would like to re-emphasize one or two of the points that he has made on the basis of our own experience. I think that it is a very practical problem in that these organic phosphate anti-cholinesterases are widely utilized as insecticides. One of the distressing things about this whole problem is that many of the users and the manufacturers of these compounds have been very slow to recognize the nature of their activity.

Several years ago we picked up a paper one morning and saw that there had been deaths in a chemical factory making insecticides. Inquiry revealed that they were making insecticides. Inquiry revealed that they were making parathion. It was stated that they had definite information that this compound was not toxic to humans, although it was known to be an anticholinesterase in lower forms of life and that was the basis for its use as an insecticide.

We inquired at the medical examiner's office and were able to get tissue from these individuals and showed that they had complete loss of cholinesterase activity.

We looked into the matter further and within this one chemical company, over the preceding several months, there had been other deaths. These deaths had been listed as due to heat stroke because they found no other cause of the death and were so completely in the dark.

The accident we studied illustrated several important points that Dr. Holmes has brought out. These people had been working there for a number of months and undoubtedly had had repeated small exposure, so that they had marked lowering of their red cell cholinesterase. In other words, their buffer had been largely used up and when that happens with these compounds—which are really among the most potent chemicals known, so that only a few milligrams indeed are capable of killing a human being—fractional portions of a milligram can be fatal.

On the day of the accident the only difference in technique was that there was a sudden heat wave. The local temperature went up about twenty degrees and that increased vaporization of the material, and inhalation of that increased amount caused a very rapid effect in several individuals.

To illustrate how potent these compounds are, there was a recent accident that happened to a research worker using this material. One of these compounds was shipped to this individual and during transport there had been an invisible leakage from the container so that there was no way of seeing that the container had leaked.

He opened the container, handled it with every precaution, and yet he unknowingly breathed in some of the vapor, and was critically ill for several days.

Even when there is known exposure and it is recognized that it is an anticholinesterase agent, the average information available to the practicing physician in regard to treatment is slim. What he does is go to his pharmacology book on the shelf—one that may have been written a decade ago—and look up the dose of atropine which is, to put it mildly, really homeopathic in the face of exposure to these compounds.

In one seriously exposed, it may require up to 40 mgs. of atropine in the course of a day to handle the central nervous system effects, to help combat the difficulty with overwhelming bronchial secretion in these patients. Artificial respiration of some type may be needed in severe cases.

We have also seen instances in which there was suspected exposure and those who were observing the situation were well aware of the need for large doses of atropine. They did not recognize that the exposure was mild and treated the patients with 15 to 20 mgs. of atropine in the course of twenty-four hours. If patients are allowed to stand after large doses of atropine, they get considerable drop of blood pressure, and they may have difficulties because of nervous system effects, but it is amazing what large doses of that material the human subject can survive.

PRESIDENT WOOD: Thank you, Dr. Harvey. Is there any further discussion?

DR. GAMMON (Philadelphia): I think we owe a debt to Dr. McGee and Dr. Holmes for bringing this to our attention. We are living in an environment which is constantly shifting through the introduction of new toxic compounds into agriculture, and it is a little difficult to get up-to-date information about these agents. In dealing with certain problems of the central nervous system, we must inquire about these exposures and we learn that gardening and farming are not the innocuous occupations they were once considered to be.

There are others in different classes: For example, arsenical poisoning among tobacco growers in North Carolina, and there is another organic mercurial used as a fungicide for wheat called Ceresin, which has been blamed for causing the condition called amyotrophic lateral sclerosis.

And thus we are constantly asking ourselves for evidences of toxic symptoms, and this type of inquiry is not always innocuous, as I found out when I tried to discover what they were using in a mushroom farm in the way of insecticides, this farm being worked by Puerto Rican imported labor. Later a man called up and said in desperation that I had planted the idea that he was poisoning their workers and they were all just about ready to return to Puerto Rico, all hundred of them. So, this effort is not always to be undertaken lightly.

Perhaps one ought to cite one other observation about cholinesterase poisoning, and that is in the treatment of myasthenia where an overdose will cause paralysis frequently undistinguishable from the disease itself and unless recognized ending in fatality.

I should like to ask Dr. Holmes if there are any compounds capable of dissociating these agents from cholinesterase in the blood or red cells? In other words, is there another type of treatment other than atropine?

DR. HOLMES (Closing): As concerns other therapeutic compounds, I am not in a position to say too much about them. Most of you have read in the paper that certain chemical compounds have been developed which will, when administered to animals, either prevent the union of these organic phosphorus agents with the cholinesterase or even cause some dissociation. So far they are not practical thera-

peutically, I believe, because of the large dosages that must be used in the experimental animal.

I think recognizing exposure to these agents as pointed out by both Dr. Harvey and Dr. Gammon is very important. Our most tragic accidents have been in children who got hold of these compounds accidentally. In one case cited, the child had the first symptoms at two o'clock in the afternoon and died at eight-thirty in the evening. The attending doctor did not recognize the nature of his illness. Yet, there probably would have been adequate time for definitive therapy since the child was first seen medically at two-thirty in the afternoon.

I was a bit disturbed recently. We have a law in Colorado that all insecticides sold in the state must be registered with the Department of Agriculture together with a listing of their composition and their antidote. I was surprised recently to discover when I called up the responsible bureau that the law had not been rigidly enforced, and no information was available on an insect repellent to which a young child had just been exposed. This emphasizes the importance of having available to the medical profession of the community adequate information about insecticides and other commercial chemicals.

I would like to emphasize one other aspect. People tend to become careless when using these agents day after day. As a matter of fact, our Professor of Industrial Medicine had a mild exposure when using an insecticide at home last summer and yet he is well acquainted with these agents. A good example is the story of a farmer over on the Western Slope of the Rockies who had been using these agents as insecticides for four years very carefully, and had never suffered an exposure. For this reason he felt they were not as potent as everybody had stated, and decided to spray his cow-barn with one of these agents. He had just paid several thousand dollars for a prize breeding bull and the new bull turned over on its back and died as a result of the spraying. He has been very careful since that time.

I think that men working with these materials must continuously be careful. In Colorado where men are working with these agents, I have asked that periodic blood samples be sent to us. Thus, if there is any indication that the men are absorbing significant amounts of the agent, we can discover it before serious exposure occurs. We may receive ten or more blood samples a week during the periods of active spraying. In this way we have helped considerably in pointing out to the doctor which men might get into serious trouble, which men are suffering mild exposure and which men are using the material with complete safety.